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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 04/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/848,159	YUAN ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) 7-10,13-15 and 17-21 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6,11,12,16 and 22-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1–26 are pending.

Claims 7-10, 13-15, and 17-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 1-6, 11, 12, 16, and 22-26 have been examined herein to the extent they read on the elected species, AGN 194310 (also known as 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2H)-thiochromen-6-yl]-ethynyl]-benzoic acid.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are 22-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for RAR antagonists and inverse agonists disclosed in page 6 – 21 of the instant specification, does not reasonably provide enablement for other RAR antagonists and inverse agonists. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have

required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that define neither a "RAR antagonist" nor an "RAR inverse agonists". Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "RAR antagonist" and "RAR inverse agonists" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required because they are not structurally related and the instant specification fails to provide enough guidance and information for one of skilled in the art to ascertain these compounds. In other words, the instant specification merely describes functionally what compounds will do without disclosing what they really are. The instant claims read on all "RAR antagonist" or "RAR inverse agonists", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Please note that the

compounds encompassed by the instant claims are more than the compounds disclosed in the instant specification. Without sufficient guidance provided in the instant specification, every compound known to man would be a potential candidate for the instant invention. One of skilled in the art would then be required to screen every known compounds in order to practice the full scope of the invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

Response to Arguments with regard to 35 USC 112, first paragraph

Applicant's arguments filed February 2, 2004 averring "whether claims necessitate an exhaustive search is irrelevant in properly establishing an enablement rejection under 35 USC 112" have been fully considered but they are not persuasive. If considered such factor only, it may not be enough to establish an enablement rejection under 35 USC 112. However, as discussed above, the claims herein recite compounds that are not even envisioned by the applicant. There is no guidance as to how to obtain these compounds disclosed in the instant specification. Moreover, there is no activity-structure relationship between a RA receptor modulators and RA receptor disclosed in the instant specification. Thus, an exhaustive and undue search in order to ascertain the compounds suitable for practice in the instant invention would have been performed.

Applicant's arguments filed February 2, 2004 averring "the two classes of compounds do not indicate that every compound known to man would be a candidate" have been considered, but are not found persuasive. As discussed above, there is no activity-structure relationship between a RA receptor modulators and RA receptor

disclosed in the instant specification. In other words, what makes one compound as a RAR antagonist, but not a RAR agonist? Or what makes another compound a RAR inverse agonist but not a RAR antagonist? There is no guidance as to how to obtain these compounds disclosed in the instant specification. Examiner notes that the instant claims encompass compounds, which are not even envisioned by the applicants. Without the specific guidance as to how to ascertain these compounds, every compounds known to man would be a potential candidate [emphasis added]. Thus, one of skilled in the art would have to perform undue experimentation to ascertain compounds suitable for use in the instant invention.

Applicant's arguments filed February 2, 2004 averring enough guidance being disclosed in the instant specification have been considered, but are not found persuasive. Applicants argue that over 15 pages of examples of suitable RAR antagonists and inverse agonists are disclosed in the instant specification and therefore, one of skilled in the art would be able to perform experimentation to ascertain the suitable compounds without undue experimentation. Examiner notes that the RAR compounds listed in the page 6-21 are merely examples, not guidance. As discussed above, the instant claims encompass compounds, which are not even envisioned by the applicants. Furthermore, there is no activity-structure relationship between a RA receptor modulators and RA receptor disclosed in the instant specification. Without the specific information, undue experimentation is required to perform in order for the skilled artisan to practice the full scope of the herein claimed invention.

Applicant's arguments filed February 2, 2004 averring the eight factors in *In re Wands* not being required to assess whether the disclosure would require experimentation by citing *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* have been considered, but are not found persuasive. Examiner notes that the court in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* ruled that "it is not necessary that a court review all the *Wands* factors to find a disclosure enabling" [emphasis added]. In the instant case, it is also not necessary to review all *Wands* factors for one of skilled artisan to see the instant specification's failure to meet the requirements under 35 USC 112, first paragraph. As discussed above, it is clear that not enough guidance is disclosed to ascertains a suitable compounds other than those listed in pages 6-21. Only two working examples, AGN 194310 and AGN 197116 are demonstrated their effectiveness on affecting patient's lipid profile. It is not known in the art what activity-structure relationship between the RAR modulators and the receptor site would be. In view of the above, the claims are considered properly rejected under 35 USC 112, first paragraph.

Claims 1-6, 11, 12, 16, and 22-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation "without coadministering a retinoid to said mammal" recited in claims 1 and 25 is not supported by the originally filed specification or originally filed claims. The instant claims

specifically exclude one specific agent in the method of treating hyperlipidemia. Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. [emphasis added] See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977). See also MPEP 2163 and 2173.05(i).

Response to Arguments with regard to new matter rejection

Applicant's rebuttal arguments filed February 2, 2004 averring Examiner's admission of record that the present specification contains a description of administration of a RAR antagonist or inverse agonist without coadministration of a retinoid have been considered, but are not found persuasive. Examiner notes that Applicant mischaracterizes Examiner's statement in the previous office action mailed June 2, 2003. Applicant simply pulls out one sentence out of the context in the previous office action. In the previous office action mailed June 2, 2003 at page 3, 2nd full paragraph, Examiner is trying to response to the applicant and explain why the new matter rejection stated in that office action, which is difference than that set forth in the instant office action, is considered proper. The scope of the claims as recited in December 22, 2002 is not the same as that of the instant claims. The new matter rejection set forth in the office action mailed June 2, 2003 is directed to the recited limitation "to treat hyperlipidemia caused other than by the administration of retinoids to the mammal" in claim 1 in amendments filed May 22, 2002; whereas the instant new matter rejection is directed to the limitation "without coadministering a retinoid to said

mammal". In view of the whole context of the office action of record, the statement "the basis of the new matter rejection is not because the specification fails to describe the coadministration of retinoid and the compounds herein" [emphasis added] should be construed as "the basis of the new mater rejection is not based on the specification's failure to describe the coadministration of retinoid and the compounds herein" (See the previous office action mailed June 2, 2003 at page 3, 2nd full paragraph). The claims are still considered properly rejected under 35 USC 112, first paragraph.

Applicant's rebuttal arguments filed February 2, 2004 averring the examples 7 and 8 demonstrating the administering RAR modulators without coadministered retinoids have been considered, but are not found persuasive. Examiner notes that the examples 7 and 8 in the instant specification merely demonstrate the administration of RAR antagonist or inverse agonist alone. The scope of administering RAR antagonist or inverse agonist alone is different than that of administering RAR antagonist or inverse agonist without coadministering a retinoids. The instant claims specifically exclude one specific class of agents. Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977). See also MPEP 2163 and 2173.05(i). In view of the above, the claims are still properly rejected under 35 USC 112, first paragraph.

Applicant's rebuttal arguments filed February 2, 2004 with regard to written description have been considered, but are not found persuasive. Examiner believes the

burden has shifted to the applicant because the Examiner has detailed his reasoning for the new matter rejection. There is no support for the herein recited limitation "without coadministering a retinoid to said mammal". Applicant is recommended to demonstrate the disclosure in the originally filed specification or originally filed claims that contain such limitation. Absent such showing, the rejection is considered proper under 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6, 11, 12, 16, and 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klein et al. (US Patent 5,776,699) in view of Lenhard et al. (Biochemical Pharmacology, 2000;59:1063-1068) and Aberg et al. (Atherosclerosis,

1985; 54:89-97), Klein et al. and Aberg et al. are references of record in the previous office action mailed October 2, 2001.

Klein et al. teaches a group of RAR antagonists broadly, including the elected compound AGN 194310, being useful in inhibiting hypertriglyceride that are induced by the RAR receptor activation (See particularly Col. 3, line 45-col. 4, line 49; also col. 20, line 67).

Klein et al. does not expressly teach the employment of 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2H)-thiochromen-6-yl]-ethynyl]-benzoic acid specifically in the method of lowering triglyceride. Klein et al. does not expressly teach the employment of 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2H)-thiochromen-6-yl]-ethynyl]-benzoic acid to prevent myocardial infarction.

Lenhard et al. teaches HIV protease inhibitor Indinavir promoting dyslipidemia by increasing RAR signaling (See the abstract, also page 1067, col. 2). Lenhard et al. also teaches the employment of RAR antagonist 193109 can block the RAR signaling activation caused by indinavir (See the abstract).

Aberg et al. teaches that elevated serum triglyceride is one of the risk factor of developing myocardial infarction (See particularly page 89, third para.; also page 93, Table 1 and page 95, Table 3).

It would have been obvious to one skill in the art when the invention was made to employ AGN 194310 in a method to lower triglyceride level and prevent myocardial infarction.

One of ordinary skill in the art would have motivated to employ 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2H)-thiochromen-6-yl]-ethynyl]-benzoic acid in a method of lowering triglyceride level and preventing myocardial infarction because the RAR antagonists of Klein et al. are known to be useful in inhibiting hypertriglyceridemia caused by RAR activation. Therefore, employing any RAR antagonists of Klein et al., including 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2H)-thiochromen-6-yl]-ethynyl]-benzoic acid, would have been reasonably expected to be useful in a method of lowering triglyceride level that caused by RAR activation such as the administration of indinavir. Furthermore, it is known that elevated serum triglyceride increases the risk of developing myocardial infarction in patients. Therefore, patients taking 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2H)-thiochromen-6-yl]-ethynyl]-benzoic acid to lower their serum triglycerides level would be reasonably expected to prevent the development of myocardial infarction.

Response to Arguments with regard to 35 USC 103(a)

Applicant's arguments filed February 2, 2004 averring the rejection being withdrawn by the Examiner have been fully considered but they are not persuasive. Please note that the rejection is apparently overlooked by the applicant. The rejection under 35 USC 103(a) set forth in the previous office action mailed October 31, 2003 is based on a new ground of rejection. The claims are rejected over Klein et al. in view of Lenhard et al. and Aberg et al. instead of over Klein et al. in view of Aberg et al. Lenhard et al. is added in the rejection set forth in the previous office action mailed

October 31, 2003. Applicant's arguments filed February 2, 2004 would be considered irrelevant to the ground of rejection set forth in the previous office action mailed October 31, 2003.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

San-ming Hui
Patent Examiner
Art Unit 1617